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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/350,327 07/09/99 RANDOLPH

T 47-99

EXAMINER

HM22/0731

GREENLEE WINNER AND SULLIVAN PC  
5370 MANHATTAN CIRCLE SUITE 201  
BOULDER CO 80303

GUTTMAN, H

ART UNIT

PAPER NUMBER

1651

DATE MAILED:

07/31/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

**Office Action Summary**

Application No.

09/350,327

Applicant(s)

RANDOLPH ET AL.

Examiner

Harry J Guttman

Art Unit

1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 25 May 2001.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-10, 21 and 22 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-10, 21 and 22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All   b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)                      4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)                      5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 11.                      6) ☐ Other: \_\_\_\_\_

## DETAILED ACTION

### ***Status of the Application and Claims***

Claims 1-10, 21 and 22 are pending.

The Response with amendment and Declaration by Dr. Randolph filed May 25, 2001 have been received and entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Claim Rejections - 35 USC § 112***

Amended claims 1-10 and new claims 21 and 22 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The response argues that the declaration of Dr. Randolph shows that rh-IFN- $\gamma$  adds to the "list of proteins now shown to be susceptible to high pressure disaggregation/ refolding". The response implies that this singular demonstration is sufficient to provide enablement for all proteins.

The declaration of Dr. Randolph demonstrates (in much greater detail than the application) the procedure for disaggregating and refolding rh-IFN- $\gamma$ .

The amended claims recite the application of a pressure treatment that can be used to renature all proteins. However, the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use this method commensurate in the scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

The breadth of the claims reads on a procedure that can be used on any aggregated protein mixture to produce active protein of any type (e.g. monomeric, oligomeric, membrane bound, membrane associated, filament-forming, metal binding, highly allosteric, DNA binding, RNA binding, RNA containing, the numerous enzyme classes, porphyrin-containing, metal cluster-containing, disulfide bond containing etc...). The claims read on a high pressure step followed by a low pressure step. The claims have been broadened by amendment to read on a single pressure step without the use of a chaotropic agent.

It is well known in the art that most proteins, if denatured or aggregated in an inclusion body, do not readily renature using a single method of treatment. Some

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proteins, if denatured or aggregated in an inclusion body, have no treatment that can be used to yield active protein (e.g., insulin and other multimeric proteins). It is well known that proteins are easily misfolded. For example, the article of Wolynes and coworkers (i.e., Onuchic et al. (1997)) discusses the protein folding pathway as possessing many dead ends (i.e., improperly folded states; see Fig.5). In the introduction of Hevehan et al. (1997), they discuss the common aggravation of inclusion body formation (i.e., the aggregation of improperly folded proteins) from recombinant protein synthesis. These are only a small sample of literature that clearly demonstrates the unpredictable nature of the art. Thus, while it may be possible that the procedure, as described in the claims, could be useful for a limited number of proteins, it seems highly unlikely that this procedure could be used for all types of proteins even after extensive experimentation.

There is no guidance from the application as to what extent the pressure should be applied in the first step for a given protein (or type thereof), nor to what extent the pressure should be decreased in the second step for a given protein (or type thereof). Given that the pressure is critical to this invention, it should be discussed and specified to give direction on how it should be chosen for a proper working embodiment of the invention for an adequate number of protein types. Thus given high level of unpredictability in the art, as described above, one of ordinary skill in the art at the time of the invention would require a substantial inventive contribution to practice the invention, especially with its current breadth.

Finally, applicant presents no working embodiment in the application of the two-step pressure disaggregation process. The examples in the application were described

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in the previous action; it is noted that the one-step pressure example does not provide enablement for the scope of the claims because the claims clearly encompass a two-step process. To date, the only demonstration of the two-step pressure process is given in the Declaration of Dr. Randolph. This exemplification represents a single example of a single protein type in the vast array of proteins and protein types (see examples above). While this singular, narrow working embodiment can not be a sole factor in determining enablement, its limited demonstration compared to the scope of the claims, in light of (a) the unpredictable nature of the art and (b) the lack of direction provided by the application, provides additional weight to the lack of enablement in consideration of the Wands factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention.

Applicant's arguments filed May 25, 2001 have been fully considered but they are not found persuasive for the reasons of record and for the additional reasons above.

***Claim Rejections - 35 USC § 102***

Amended claims 1-3 are now rejected under 35 U.S.C. 102(b) as being clearly anticipated by Zong et al. (1995).

Zong et al. (1995) disclose the use of 2 kbar pressure step with the addition of oxidized glutathione and dithiothreitol to refold recombinant chloroperoxidase from a pellet (page 12422 column 2 and table 1).

Applicant's arguments filed May 25, 2001 have been fully considered but they are not found persuasive for the reasons of record and for the additional reasons above.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Additional references not cited in this action have been listed in PTO-892 to establish the state of the art.

Any inquiry concerning this communication should be directed to Harry J. Guttman, Ph.D. at telephone number (703) 305-0159. The examiner can normally be reached during the hours of 07:30 to 16:00 Eastern Time, Mon.-Thurs. If attempts to reach the examiner by telephone are unsuccessful, a message may be left on the voice mail. The fax number for Art Unit 1651 is (703) 308-4242 or 305-3014. Any inquiry of a

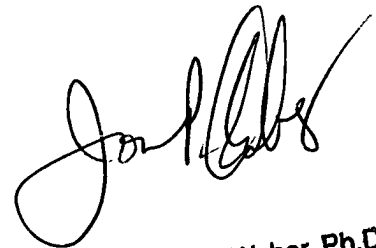
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general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. My supervisor, Michael Wityshyn, may be contacted at (703) 308-4743.

All internet e-mail communications will be made of record in the application file. PTO employees will not communicate with applicant via internet e-mail where sensitive data will be exchanged or where there exists a possibility that sensitive data could be identified or exchanged unless there is of record an express waiver of the confidentiality requirements of 35 U.S.C. 122 by the applicant. See the Interim Internet Usage Policy published in the Patent and Trademark Office Official Gazette on 25 February 1997 at 1195 OG 89.

H.J.G. 30 July 2001

Harry J. Guttman, Ph.D.  
Examiner, 1651  
harry.guttman@uspto.gov

A handwritten signature in black ink, appearing to read "Jon P. Weber", with a large, stylized initial "J" and a long, sweeping horizontal stroke extending to the right.

Jon P. Weber, Ph.D.  
Primary Examiner